DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 25, 2010 has been entered. Claims 1, 2 and 6 (currently amended), 3, 4 and 7-33 (original or previously presented) and 34-43 (newly added) will be examined on the merits. Claim 5 has been canceled.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 9 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 recites the limitation "partial sequences formed in step (c)" allegedly cited in base claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "or of the joined nucleic acid double strands" allegedly cited in base claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-4, 6-14, 19-27 and 32-39 are rejected under 35 U.S.C. 102(e) as being anticipated by Bernard et al. (U.S. Patent Pub. No. 2004/0203085).

With regard to claims 1 and 37, Bernard teaches a method for preparing at least one complementary copy of specified sequences of support-bound single-stranded nucleic acids (a method is presented for highly parallel preparation of molecule libraries on a substrate surface, for overview, see Abstract, paragraph 1, lines 1-3 and paragraph 6, lines 1-8), comprising the steps:

(a) providing a support with a surface which comprises a plurality of positions at each of which different nucleic acid fragments are in-situ synthesized such that said fragments comprise base sequences which (1) are chosen to be complementary to the specified sequences of nucleic acids to be prepared (array molecules are prepared as

template DNA by in situ DNA polymerization on a substrate surface to be complementary to the target sequences to be prepared, paragraph 51, lines 1-10 and Figure 2A, parts 1 and 2) and (2) which comprise a primer site proximal or distal to the support (the template DNA comprises a primer binding sequence at the 3' end of the template, distal to the support, paragraph 55 and paragraph 56, lines 1-3; note, the primer binding sequence may bind away or distal from substrate surface if the template DNA is a 5'-attached template, paragraph 51, lines 10-13, as shown in Figure 2A, but would be proximal to the support when the DNA is attached via its 3' end, paragraph 63, lines 1-6),

(b) adding nucleotide building blocks, an enzyme, and a primer complementary to said primer site which brings about generation of different single-stranded nucleic acids from the complementary base sequences from (a) (the substrate loaded with template DNA sequences is then incubated with a cocktail comprising a universal primer, a DNA polymerase and nucleotides, paragraph 56, lines 1-9),

(c) generating at least one single-stranded complementary copy of the nucleic acids to be prepared in (a) (the template DNA sequences on the array are replicated in a parallel reaction after addition of the primers, DNA polymerase and nucleotides, paragraph 56, lines 9-13 and Figure 2B), and

(d) detaching the single-stranded nucleic acids generated in step (c) and, where appropriate, providing for further operations (the freshly synthesized copy DNA hybridized to the template DNA is destabilized by detergents, salts, pH or temperature and transferred to a second substrate via an anchor, paragraph 56, lines 13-22 and

Figures 2C and D; prepared arrays may be used for a variety of analytical purposes, including applications in medical and veterinary diagnostics, forensics and drug development, paragraph 38, lines 1-8).

With regard to claim 2, Bernard teaches a method for preparing a predetermined nucleic acid double strand having its sequence specified by a user (arrays prepared from original template DNA and transferred to a new surface are then used for preparing double-stranded DNA, paragraph 58, lines 1-19 and Figure 3D), comprising the steps:

(a) providing a support with a surface which comprises a plurality of positions at each of which different nucleic acid fragments are in-situ synthesized such that said fragments comprise base sequences which (1) are chosen to be complementary to partial sequences of the nucleic acid double strand having a user-specified sequence to be prepared (array molecules are prepared as template DNA by in situ DNA polymerization on a substrate surface to be complementary to the target sequences to be prepared, paragraph 51, lines 1-10 and Figure 2A, parts 1 and 2;) and (2) which comprise a primer site proximal to the support (the template DNA comprises a primer binding sequence at the 3' end of the template, paragraph 55 and paragraph 56, lines 1-3; note, the primer binding sequence may bind away from substrate surface if the template DNA is a 5'-attached template, paragraph 51, lines 10-13, as shown in Figure 2A, but would be proximal to the support when the DNA is attached via its 3' end, paragraph 63, lines 1-6),

(b) adding nucleotide building blocks, an enzyme and a primer complementary to the primer site which brings about generation of complementary copies of the base sequences from (a) (the substrate loaded with template DNA sequences is then incubated with a cocktail comprising a universal primer, a DNA polymerase and nucleotides, paragraph 56, lines 1-9 and paragraph 58, lines 11-13),

(c) generating single-stranded complementary copies of the nucleic acids to be prepared in (a) (the copy DNA is synthesized on the original template DNA by a DNA polymerase in a primary extension reaction, paragraph 58, lines 11-13 and Figure 3B), and

(d) assembling the single-stranded partial sequences generated in step c) to give the desired nucleic acid double strand (the single-stranded products may be transferred to a new substrate a copied to produce double-stranded products at each site of the array, paragraph 58, lines 13-18 and Figure 3C and D).

With regard to claims 3 and 4, Bernard teaches a method characterized in that the support is selected from flat supports, porous supports, reaction supports with electrodes, reaction supports with particles or beads, microfluidic reaction supports which optionally have surface modifications such as gels, linkers, spacers, polymers, amorphous layers or/and 3D matrices, and combinations of the aforementioned supports (the microarray surface may be plastic, metal or glass or a polymer with elastic properties and may be flat, roller-shaped, curved or convex, paragraph 10, lines 1-14 and paragraph 33, lines 1-3; the surfaces may also have light and electric field-conducting properties, paragraph 12, lines 1-7 and paragraph 13, lines 1-2; the surfaces

are capable of having a plurality of spots of complex molecules in a definable spatial pattern, wherein each spot is available for carrying out reactions when a polymerization cocktail is added, paragraph 21, lines 1-11 and paragraph 56, lines 6-9).

With regard to claims 6 and 7, Bernard teaches a method characterized in that the nucleic acid fragments from (a) are synthesized by spatially or/and time-resolved illumination by means of a programmable light source matrix within the chambers of one or more reaction zones within a fluidic reaction chamber (particular molecules such as nucleic acid molecules are selectively synthesized in a space-resolved manner at predefined locations such as in a dot matrix via location-selective light conduction, paragraph 8, lines 1-6, paragraph 12, lines 4-7 and paragraph 32, lines 5-7).

With regard to claim 8, Bernard teaches a method characterized in that the assembly of the partial sequences in step (c) takes place at least partly in one or more steps on the support (the copy DNA is prepared on the support using the original template DNA to synthesize the copy DNA product using a DNA polymerase in a primary extension reaction, paragraph 58, lines 11-13 and Figure 3B).

With regard to claim 9, Bernard teaches a method wherein the nucleic acid fragments from (a) are chosen so that the nucleic acids or partial sequences formed in step (c) can be joined to give nucleic acid double-stranded hybrids (preparation of double-stranded nucleic acid hybrids may be formed by hybridizing small RNA fragments with random sequences to original DNA on the arrays, and ligating the sequences together to form an RNA strand complementary to the original DNA, paragraph 80, lines 3-9).

With regard to claims 10 and 11, Bernard teaches a method wherein a plurality of nucleic acids or partial sequences which form a strand of the nucleic acid double strand are covalently connected together comprising a treatment with ligase (random RNA sequences can be covalently assembled together on the original DNA template strands of the array by ligation using T4 RNA ligase, paragraph 80, lines 3-9).

With regard to claim 12, Bernard teaches a method characterized in that step (b) comprises the addition of at least one primer for each position of the support, the primer being complementary to part of the nucleic acid fragment located at this position and step (b) comprising an elongation of the primer (each fragment attached to each position on the array contains a primer binding site for a universal primer so that all sequences on the array are replicated in parallel upon addition of a cocktail comprising a universal primer, a DNA polymerase and nucleotides, paragraph 56, lines 1-9 and Figure 2B).

With regard to claims 13 and 14, Bernard teaches a method characterized in that double-stranded nucleic acid fragments are provided in step (a), with at least one strand being tethered to the surface of the support and step (b) comprises transcription of double-stranded DNA fragments or/and replication of double-stranded RNA fragments (double-stranded nucleic acid fragments may be provided on the array surface for a transcription reaction to produce RNA copies complementary to one of the strands of the template attached to the surface, paragraph 79, lines 4-7, paragraph 80, lines 1-3 and Figure 6B and C).

With regard to claim 19, Bernard teaches a method characterized in that the nucleic acid fragments from (a) are generated by: provision of capture probes at the positions (adaptor sequences are ligated to original DNA strands attached to array surface positions, to allow transfer of the fragments to a new surface, and attachment of second adaptors to the opposite end of the fragments, paragraph 60, lines 1-9 and 19-25 , paragraph 61, lines 1-2 and Figure 4B-E; fragments may also be attached to array positions via anchoring groups on the fragment that are complementary to oligonucleotide capture probes attached to the array, paragraph 52, lines 1-3) and binding of nucleic acid fragments from a fluid passed over the support to the capture probes, where the capture probes are complementary to partial regions of the nucleic acid fragments (a universal primer in a polymerization a cocktail is hybridized to the second adaptor and extended to form a copy of the original DNA strand, paragraph 61, lines 2-10 and Figure 4F-G).

With regard to claims 20 and 32, Bernard teaches a method wherein recognition sequences for specific interaction with molecules such as proteins, nucleic acids, peptides, drugs, saccharides, lipids, hormones or/and organic compounds are present at one or more positions in the sequence of the generated nucleic acids (sequences of the fragments generated on the arrays may contain recognition sites for restriction endonucleases, paragraph 60, lines 9-11, RNA polymerase promoter sequences may be added to array sequences, paragraph 79, lines 10-21, and RNA sequences may be generated on the array with ribosomal binding sites and a start codon, paragraph 69, lines 1-4).

With regard to claims 21 and 33, Bernard teaches a method wherein the sequence of the generated nucleic acids is a naturally occurring sequence, a non-naturally occurring sequence or a combination thereof (DNA fragments on the array may be naturally occurring, such as those comprising restriction endonuclease recognition sites and promoter sequences, paragraph 60, lines 9-11 and paragraph 79, lines 10-21, as well as non- naturally occurring sequences such at thio-RNA sequences, paragraph 66, lines 6-13).

With regard to claim 22, Bernard teaches a method characterized in that the sequence is taken from a database, from a sequencing experiment or from an apparatus for integrated synthesis and analysis of polymers (arrays can be synthesized to contain functional macromolecules by an automated in situ synthesis process to produce fragments containing known elements such as restriction sites and promoter sites, paragraph 48, lines 1-9, paragraph 60, lines 9-11 and paragraph 79).

With regard to claim 23, Bernard teaches a method characterized in that the nucleotide building blocks may comprise naturally occurring nucleotides, modified nucleotides or mixtures thereof (primers hybridized to the original DNA template strands are extended using a DNA polymerase and nucleotides, paragraph 56, lines 6-13; templates may include modified nucleotides to form PNA, paragraph 34, lines 1-8, and RNA fragments may comprise modified nucleotides to form thio-RNA, paragraph 66, lines 6-13).

With regard to claims 24 and 25, Bernard teaches a method characterized in that modified nucleotide building blocks are used for labeling and subsequent detection of

the nucleic acids or of the joined nucleic acid double strands in a light-dependent or/and electrochemical manner (fragments on the array may comprise labels or haptens such as biotin, digoxigenin and FITC for transferring copied products to new substrates, and may be detected at exact positions on the array using labels on the substrate, paragraph 16, lines 1-21 and paragraph 21, liens 8-11).

With regard to claims 26 and 27, Bernard teaches a method wherein said prepared nucleic acids are tools for therapeutic, pharmacological or diagnostic purposes (prepared arrays may be used for a variety of analytical purposes, including applications in medical and veterinary diagnostics, forensics and drug development, paragraph 38, lines 1-8).

With regard to claim 34, Bernard teaches a method wherein said nucleic acid fragments on said support surface are synthesized under software control (arrays containing nucleic acid fragments are prepared by a sequential de novo synthesis in situ using an apparatus that performs the steps automatically, paragraph 48, lines 1-9 and claim 29).

With regard to claims 35, 36, 38 and 39, Bernard teaches a method wherein the primer site is a RNA promoter (primers used in copying original template DNA may comprise an RNA polymerase promoter sequence such as the T7 promoter, paragraph 79, lines 7-13).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 15-18 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernard et al. (U.S. Patent Pub. No. 2004/0203085) in view of Chetverin et al. (U.S. Patent No. 6,322,971).

Bernard teaches the limitations of claims 1-4, 6-14, 19-27 and 32-39, as discussed above.

In addition, with regard to claim 40, Bernard teaches a method for preparing at least one copy of specified sequences of support-bound single-stranded nucleic acids (a method is presented for highly parallel preparation of molecule libraries on a

substrate surface, for overview, see Abstract, paragraph 1, lines 1-3 and paragraph 6, lines 1-8), comprising the steps:

(a) providing a support with a surface which comprises a plurality of positions at each of which different nucleic acid fragments are in-situ synthesized such that said fragments comprise base sequences which (1) are chosen to be complementary to the specified sequences of nucleic acids to be prepared (array molecules are prepared as template DNA by in situ DNA polymerization on a substrate surface to be complementary to the target sequences to be prepared, paragraph 51, lines 1-10 and Figure 2A, parts 1 and 2),

(b) adding nucleotide building blocks and an enzyme which brings about generation of different single-stranded nucleic acids from the complementary base sequences from (a) (the substrate loaded with template DNA sequences is then incubated with a cocktail comprising a universal primer, a DNA polymerase and nucleotides, paragraph 56, lines 1-9),

(c) generating at least one single-stranded complementary copy of the nucleic acids to be prepared in (a) (the template DNA sequences on the array are replicated in a parallel reaction after addition of the primers, DNA polymerase and nucleotides, paragraph 56, lines 9-13 and Figure 2B), and

(d) detaching the single-stranded nucleic acids generated in step (c) and, where appropriate, providing for further operations (the freshly synthesized copy DNA hybridized to the template DNA is destabilized by detergents, salts, pH or temperature and transferred to a second substrate via an anchor, paragraph 56, lines 13-22 and

Figures 2C and D; prepared arrays may be used for a variety of analytical purposes, including applications in medical and veterinary diagnostics, forensics and drug development, paragraph 38, lines 1-8).

With regard to claims 41-43, Bernard teaches a method wherein the primer site is a RNA promoter such as a T7, T3 or SP6 promoter (primers used in copying original template DNA may comprise an RNA polymerase promoter sequence such as the T7 promoter, paragraph 79, lines 7-13).

However, Bernard does not teach a method characterized in that nucleic acid fragments or double-stranded, circular fragments, comprising a self-priming 3' end, are provided in step (a), and step (b) comprises elongation of the 3' end and which comprises elimination of the elongation product. In addition, Bernard does not teach a method further comprising transferring prepared nucleic into effector cells, or wherein the prepared nucleic acids are propagatable cloning vectors. Bernard does not teach a method wherein the prepared nucleic acids are stabilized, condensed or/and topologically manipulated during a stepwise combination and joining or subsequent thereto, wherein the stabilization, condensation or/and topological manipulation is effected by functional molecules such as histones or topoisomerases

With regard to claims 15, 17 and 40, Chetverin teaches a method characterized in that nucleic acid fragments or double-stranded, circular fragments, comprising a self-priming 3' end, are provided in step (a), and step (b) comprises elongation of the 3' end (some sequences of fragments formed on the array may contain perfect repeats that

fold back on itself to serve as self-overlapping termini, which would naturally include the formation of circular type molecules, and thus can lead to extension using the same fragment as a template and thus compromise the ability to order sequence blocks, column 38, lines 26-41).

With regard to claims 16 and 18, Chetverin teaches a method which comprises elimination of the elongation product (formation of such ambiguities can be drastically reduced by using longer probes in such recursive or repetitive sequence regions, and using larger amounts of all variable oligonucleotides on the array, column 38, line 58 to column 39, line 3).

With regard to claim 28, Chetverin teaches a method further comprising transferring said prepared nucleic acids into effector cells (isolated sequences from an array can be inserted into vectors for cloning and transformation of microbial cells, column 22, lines 26-29 and column 2, lines 54-57).

With regard to claims 29 and 30, Chetverin teaches a method wherein said prepared nucleic acids are stabilized, condensed or/and topologically manipulated during a stepwise combination and joining or subsequent thereto, wherein the stabilization, condensation or/and topological manipulation is effected by functional molecules such as histones or topoisomerases (isolated sequences from an array can also be inserted into vectors for cloning, which upon transformation into microbial cells, will undergo natural condensation and topological manipulations *in vivo*, column 22, lines 26-29 and column 2, lines 54-57).

With regard to claim 31, Chetverin teaches a method wherein said prepared nucleic acids are propagatable cloning vectors (isolated sequences from an array can also be inserted into vectors for cloning, column 22, lines 26-29; transcription sites can be placed adjacent to target sequences using primers containing promoters for amplification, column 9, lines 57-60).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Bernard and Chetverin since both references teach methods for preparation of complementary copies of nucleic acid fragments at specified locations on a support surface and transfer of the newly made copies to a second surface to produce replicate arrays. While Bernard produces the template for producing the complementary copies by in situ synthesis on the array surface, Chetverin provides the template by primer extension of surface-bound primers hybridized to templates to be copied. However, in both cases, complementary copies of templates are produced by primer extension or PCR and the copies may be transferred to fresh substrates to produce replicate arrays. In fact, the original arrays may be used repeatedly for producing many replicated or copy arrays or mirror image arrays (see Bernard, paragraph 58 and Figure 3 and Chetverin, column 10, line 66 to column 11, line 4). Thus, an ordinary practitioner would have been motivated to apply the teachings of Chetverin in the methods of Bernard for preparing copies of nucleic acid fragments on array surfaces, including fragments that may contain self-priming 3' ends or double-stranded fragments with a self-priming end that may lead to formation of circular products, either of which may lead to unwanted products during synthesis

reactions, but which can be avoided or reduced by following the suggestions of Chetverin (see column 38, line 23 to column 39, line 9). In addition, Chetverin teaches additional uses of complementary nucleic copies produced on arrays, including inserting isolated sequences into cloning vectors for transformation of microbial cells (Chetverin, column 22, lines 26-29), including the insertion of promoters adjacent to target sequences using amplification primers containing promoter sequences (Chetverin, column 9, lines 57-60). One of skill in the art will recognize that similar nucleic acid copies can easily be produced by the methods of Bernard for use in such downstream processes.

Response to Arguments

9. Applicant's arguments filed October 25, 2010 have been fully considered but they are not persuasive.

Applicant argues that the rejection of claims 1-33 under 35 U.S.C. § 102(b) as being anticipated by Chetverin et al. (U.S. Patent No. 6,322,971) should be withdrawn based on amendments to the claims. In particular, Applicant argues that Chetverin does not teach a method wherein nucleic fragments on the support surface are in-situ synthesized, but rather teaches the use of an array that was obtained by immobilizing prefabricated nucleotide sequences. The Examiner agrees that the Chetverin does not teach preparation of support surfaces comprising in-situ synthesized nucleic acids and therefore the rejection is withdrawn. However, after further searching, new rejections

based on new grounds are now presented and therefore the remaining arguments are moot.

Summary

10. Claims 1-4 and 6-43 are rejected. No claims are allowable.

Correspondence

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David C Thomas/
Examiner, Art Unit 1637

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637